

Severe Euthyroid Cardiac Disease

Technique for Treatment with Radioiodine

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MORE THAN THREE HUNDRED euthyroid seriously ill patients with heart disease have been treated with radioactive iodine (I^{131}) since February, 1950, in the Radiation Therapy Department of the Cedars of Lebanon Hospital in Los Angeles.

The rationale of this treatment is to produce a state of beneficial relative hypothyroidism by lowering the total metabolism of the body, so that the heart has less work to do. This is a symptomatic treatment for patients incapacitated by heart disease who have a hopeless prognosis and who have a limited life expectancy. The organic cardiac disease is not cured by radioiodine. All other types of cardiac treatment are continued as indicated.

Radioiodine treatment for euthyroid cardiac cripples was pioneered by Blumgart³ and associates in 1947. They reported their early results in 1952. Wolferth⁹ gave account of 28 patients treated with radioiodine for angina pectoris in 1951. Jaffe, Rosenfeld, Pobirs and Stuppy^{6,7} reported their early results in November, 1951, and in 1952 reported upon treatment of a group of 100 patients. Chapman⁵ published a report in 1952 and Serber⁸ in 1953. Blumgart,⁴ in his chairman's address to the Section on Internal Medicine of the American Medical Association in June, 1954, summarized the results of treatment in 1,070 cases at 47 different clinics in the United States. All published reports by these investigators have shown favorable results following the radioiodine treatment for angina pectoris and, with the exception of Serber's all reports were also favorable for the treatment of severe congestive failure.

MULTIPLE SMALL DOSE RADIOIODINE TECHNIQUE

When Blumgart first described the radioiodine treatment for euthyroid patients severely ill with heart disease, he reported that he was giving large doses of radioiodine—as high as 42 millicuries per

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• It is possible to safely lower the basal metabolism of patients suffering from severe cardiac disease by administering multiple small doses of radioiodine in order to achieve symptomatic relief.

From the present study, multiple small doses of I^{131} appeared to be as effective as single or multiple large doses of this material and complications such as thyroiditis, temporary thyrotoxicosis and bone marrow depression were almost always avoided. No damage to the parathyroid glands or the recurrent laryngeal nerve was observed. No radiation sickness developed after therapy.

A scintigram of the thyroid gland was useful in determining the size, shape and function of the thyroid gland before and during radioiodine treatment and helped to determine the need for additional treatment. In order to prevent the distressing symptoms of the myxedema state, desiccated thyroid was administered when necessary.

In the series of 278 euthyroid patients with severe cardiac disease who were treated with radioactive iodine, results were excellent in 35 per cent of cases and good in 44 per cent. In 21 per cent there was no improvement.

dose. He also reported thyroiditis as an undesirable side effect of the large-dose treatment. The patients complained of pain in the anterior neck and some patients also showed a temporary state of hyperthyroidism, probably the result of rapid destruction of thyroid tissue and the liberation of abnormal amounts of thyroxin into the blood stream. This temporary hyperthyroidism could prove fatal to a patient with an already severely damaged heart and very little cardiac reserve.

In the present series the author wished to give the smallest dose of radioiodine that would produce the desired clinical effect. Since Blumgart at the time of his original report did not know the minimal effective dose, it was decided to follow a plan of treatment in the present series with multiple small doses of radioiodine in an attempt to accomplish

the same clinical results without producing the undesirable side effects.

Preliminary Radioiodine Studies

Each patient was completely studied medically by his physician before he was referred for radioiodine treatment. Then, before treatment was begun, an oral tracer dose of five microcuries of I^{131} was administered to the patient in the radiation therapy department and the 24-hour uptake of the thyroid gland was measured. A second dose of 500 microcuries of radioiodine was given orally after the uptake study was completed, and a "thyrogram" (scintigram¹ of the thyroid gland) was made the next day. This gave a diagram of the approximate size, shape and degree of the uptake of the entire gland. In some cases there was a single hyperactive nodule in one lobe; in some an entire lobe was overactive and there was physiological depression of function of the other lobe. (It is interesting to note that the "thyrogram" will show these abnormal findings even though the total 24-hour uptake may be within normal limits.) Radioiodine (I^{131}) averaging six millicuries per dose, was given orally each week until the patient had had a total of 30 millicuries. This was called the "first course" of treatment.

(Before the thyrogram technique was available it was necessary to rely on clinical and uptake studies and other laboratory data for the determination of the effect of the first course of radioiodine. This necessitated waiting two to three months before the post-treatment thyroid uptake test could be done, since there was too much residual radiation activity in the gland to allow doing an uptake study before the end of the two-month interval. Now it is possible to check the size and function of the gland one month after the first course of treatment.) If the patient was not improved after the first course and the thyrogram indicated that the thyroid gland was still functioning normally, a second course of five weekly oral doses of 6 mc. of I^{131} was carried out. A third thyrogram then was made and the patient's progress evaluated. (This now is done one month after the second course.) If necessary, a third course of I^{131} was prescribed, unless the patient already had signs of hypothyroidism.

The Size of the Dose

The size of the dose of radioiodine used varies from clinic to clinic. The author prefers to give 6 mc. oral doses of I^{131} at weekly intervals until the patient has received a total of 30 mc. Other clinics have given as much as 42 mc. in a single dose. The small dose technique is used to avoid the danger of suddenly releasing large amounts of thyroxin from the destroyed gland into the blood stream. This

might produce a temporary increase in metabolism which in a patient with severe cardiac disease could be detrimental, even fatal. For the more seriously ill and hospitalized patients, doses of 1 to 2 mc. of radioiodine were given daily or every other day, in order to avoid rapid destruction of the thyroid gland with serious additional strain on the heart. Another undesirable side effect of larger doses of I^{131} is radiation thyroiditis, with an increased metabolic rate. In the patients in the present series treated according to this plan of dosage, the incidence of thyroiditis was low and there was little evidence of temporary thyrotoxicosis subsequent to I^{131} therapy. Bone marrow depression is another possible hazard of massive therapeutic doses of I^{131} , but with smaller doses there appeared to be no such effect.

Apparently the radiobiological time factor in euthyroid cardiac patients treated with I^{131} is independent of the size of the single dose or total dose.² Symptomatic relief occurred in a comparable interval after a single dose of 25 mc. or five weekly doses of 6 mc. The same percentage of excellent and good results was obtained with multiple small doses of I^{131} as with the single or multiple large doses totaling 100 mc. reported by other investigators. Therefore, use of the multiple small dose technique for treating selected euthyroid patients incapacitated with cardiac disease was continued. It was noted that about 40 per cent of the patients did well with one course of 30 mc. of radioiodine treatment, 50 per cent required two courses of 30 mc. each, and 10 per cent required three courses of 30 mc. each.

Safeguards

Safeguards against radiation are necessary when any radioactive material is used therapeutically. Single doses as large as 20 to 42 mc. make the patient a focus of considerable beta and gamma ray activity, and safe treatment usually necessitates hospitalization of the patients in order that excreta may be disposed of by trained personnel. Smaller doses do not entail this problem, since I^{131} has a half-life of eight days, and therefore most patients may be treated as out-patients.

Radioiodine should be used only in a laboratory completely equipped for handling radioisotopes and having measurement instruments for calibration of the dosage.

USE OF THYROID EXTRACT AND DEGREE OF HYPOTHYROIDISM DESIRABLE

Following radioiodine treatment it is important to follow the patients carefully in order to detect the earliest symptoms of hypothyroidism. The author has prescribed thyroid extract where necessary to avoid the severe symptoms of myxedema.

This should be done even before laboratory tests have definitely indicated myxedema levels. If frank myxedema is permitted to develop, the patient may have so many complaints referable to the myxedema state that the relief of the symptoms of cardiac disease may seem less than a boon to him.

It is the opinion of the author, and is the consensus of most investigators, that no greater degree of hypothyroidism should be permitted than adequate clinical relief of cardiac symptoms requires. Wolferth⁹ and Serber⁸ have reported upon use of conservative radioiodine dosage. Serber has controlled myxedema when it developed by giving 15 to 30 mg. of thyroid extract and noted no interference with the beneficial effects of radioiodine therapy. Chapman⁵ said that myxedema should not be permitted to develop and that patients should be kept at the basal metabolic rate of -20 to -25 per cent, that plasma-bound iodine should be kept at levels of 2 to 3 gamma per cent, and that radioiodine uptake should be maintained at 10 to 20 per cent in 48 hours. Blumgart³ and associates, on the other hand, in their early reports said they had permitted pronounced hypothyroidism, and in some instances complete myxedema, to develop in order to be sure that all thyroid tissue was affected before they administered 6 to 12 mg. of desiccated thyroid daily. They adjusted the dosage of desiccated thyroid to maintain the lowest metabolic level associated with the maximum relief of cardiac disease and the minimum discomfort from myxedema. They found in some cases that treating with sufficient thyroid extract to obviate symptoms of myxedema resulted in very little cardiac improvement over the pretreatment status. They then stated that in most of the patients they administered 6 to 30 mg. of thyroid extract to maintain basal metabolic levels of -20 to -25 per cent. In the present series when patients showed symptoms of hypothyroidism, doses of 12.5 to 30 mg. of thyroid extract daily were administered. Great care was taken to avoid development of the disagreeable clinical picture of severe hypothyroidism or myxedema. In some patients thyroid tissue eventually regenerates and further radioiodine treatment is necessary. This phenomenon was confirmed by follow-up studies of I¹³¹ uptake and thyrograms made at three-month intervals.

EVALUATION OF RESULTS

The many and diverse clinical problems present in patients with severe cardiac disease affect the evaluation of beneficial results obtained from radioiodine treatment. A result may be short of complete symptomatic relief yet be considered excellent or worth while. A patient with angina pectoris decubitus who is relieved of the need to take nitroglycerin

repeatedly throughout the day and night receives real help, even though walking without pain is still impossible. A patient who may be comfortable at rest but who cannot work because of repeated attacks of angina pectoris, is greatly benefited if he is improved sufficiently to return to work. A patient with congestive failure and ascites gains much advantage if radioiodine treatment ends the necessity of repeated paracentesis and so well controls the condition that sodium restriction or the use of mercurial diuretics is sufficient.

When it is known, in individual cases, what relief has been obtained from other forms of medical treatment, and with the clinical problems of each patient known and recorded, a more accurate evaluation of the effect of radioiodine treatment is possible. The improvement in comfort, ability to care for self or to work, reduction in required drugs and decrease in dangerous attacks of acute pulmonary edema must be weighed against the disadvantages of relative hypothyroidism.

Definitions

For purposes of evaluation in the present series, Blumgart's classification was used in order to avoid confusion of terms.

1. *Excellent (pronounced improvement)*: Greatly improved over pretreatment status, with either no recurrence of symptoms or a pronounced decrease in the frequency and severity of angina pectoris or congestive failure, despite activity greater than that possible before treatment.

2. *Good or worthwhile*: Definite decrease in frequency and severity of attacks on same activity as before treatment, or ability to do considerably more with no increase in angina pectoris or congestive failure.

3. *No worthwhile improvement*.

The patients in the series were treated with radioiodine only when other forms of medical treatment did not control their symptoms. Included were patients with severe angina pectoris, with congestive failure and a combination of both.

Results

In the series of 278 euthyroid patients with severe cardiac disease, the following results were obtained: Excellent in 35 per cent, good in 44 per cent, and no improvement in 21 per cent. Of 127 patients with angina pectoris, 34 per cent had excellent and 46 per cent good results. Only 20 per cent showed no improvement. Eighty-six patients had congestive failure, and results in that group were: Excellent, 37 per cent; good, 40 per cent; no improvement, 23 per cent. For a group of 65 patients with both

angina pectoris and congestive failure results were excellent in 34 per cent of cases and good in 45 per cent. In 21 per cent there was no improvement.

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